

## **Amendments to the Specification**

Please substitute the abstract provided herein on a separate sheet, with the abstract previously submitted in this application.

Please insert the following section heading and paragraph immediately after the title:

### **CROSS-RELATION TO RELATED APPLICATIONS**

This application is a 371 application of PCT/EP2005/003663, having an international filing date of April 7, 2005.

Please insert the following section heading immediately before paragraph [003] of the application as published (US 2007/0232658 A1):

### **BACKGROUND OF THE INVENTION**

Please insert the following section heading immediately before paragraph [0064] of the application as published (US 2007/0232658 A1):

### **SUMMARY OF THE INVENTION**

Please insert the following section heading immediately before paragraph [0065] of the application as published (US 2007/0232658 A1):

### **DETAILED DESCRIPTION OF THE INVENTION**

Please insert the following immediately after paragraph [0092] of the application as published (US 2007/0232658 A1):

What is claimed is:

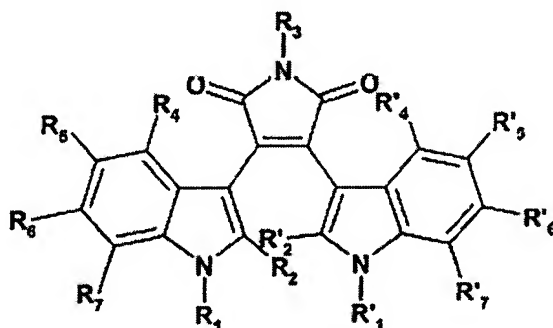
## Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

### Listing of Claims:

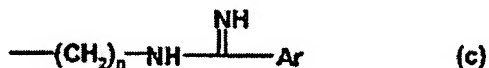
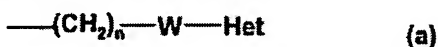
Claim 1 (currently amended): A method for treating ~~or preventing~~ organ or tissue transplant rejection or an autoimmune disease other than diabetes mellitus or for ~~preventing~~ treating graft-versus-host disease in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a protein kinase C inhibitor of formula I, II, III or IV or a pharmaceutically acceptable salt, hydrate or solvate thereof,

wherein compounds of formula I are



wherein

each of  $R_1$  and  $R'_1$ , independently, is hydrogen, alkyl, haloalkyl, alkenyl, arylalkyl, alkoxyalkyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, acyl-aminoalkyl, acyloxyalkyl, cyanoalkyl, amidinoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, or a group of the formula (a), (b) or (c)



wherein Het signifies a heterocyclyl group; W signifies NH, S or a bond; T signifies NH or S; V signifies O, S, NH, or NCN; A signifies alkylthio, amino, monoalkylamino or dialkylamino; Ar signifies aryl;

each of  $R_2$  and  $R'_2$ , independently, is hydrogen, alkyl, alkoxyalkyl, hydroxyalkyl,  $\text{C}_1\text{--C}_3$ alkylthio,  $\text{S(O)C}_1\text{--C}_3$ alkyl,  $\text{CF}_3$ ;

or  $R_1$  and  $R_2$  form together  $\text{---}(\text{CH}_2)_r\text{---X---CH}_2\text{---}$  wherein  $r$  is 1, 2, or 3, and X is  $\text{CHR}_8$  or  $\text{NR}_8$  wherein  $R_8$  is  $(\text{CH}_2)_s\text{R}_9$  wherein  $R_9$  is hydrogen, hydroxy, alkoxy, amino,

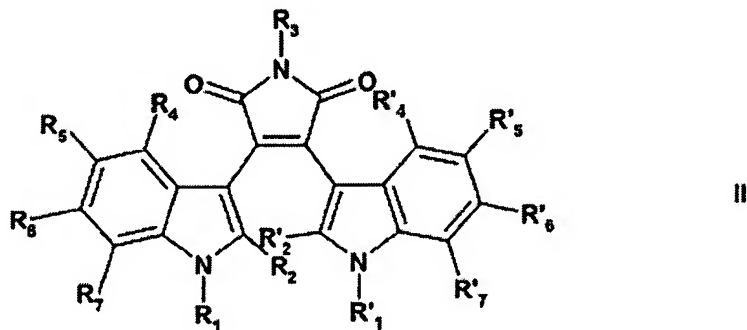
monoalkylamino, dialkylamino, trialkylamino, azido, acylamino, alkoxycarbonyl, cyano, amidino, or aminocarbonyl, and s is 0, 1, 2 or 3;

R<sub>3</sub> is hydrogen or CH<sub>3</sub>CO;

each of R<sub>4</sub>, R'<sub>4</sub>, R<sub>5</sub>, R'<sub>5</sub>, R<sub>6</sub>, R'<sub>6</sub>, R<sub>7</sub> and R'<sub>7</sub>, independently, is hydrogen, halogen, alkyl, hydroxy, alkoxy, —COO(C<sub>1</sub>-C<sub>3</sub>alkyl), CF<sub>3</sub>, nitro, amino, acetylamino, monoalkylamino, dialkylamino, alkylthio, C<sub>1</sub>-C<sub>3</sub>alkylthio, or S(O)C<sub>1</sub>-C<sub>3</sub>alkyl; and

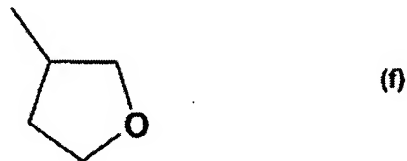
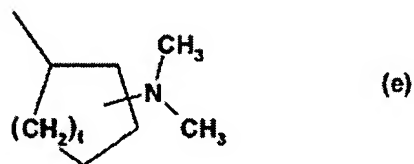
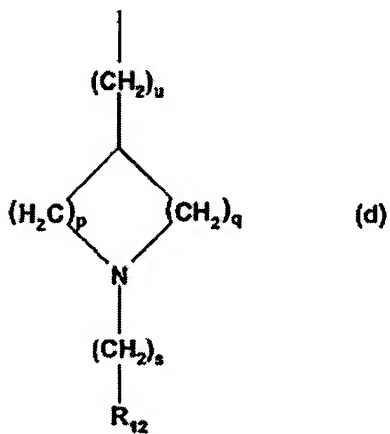
n is 1, 2, 3, 4, 5 or 6;

and compounds of formula II are



wherein

R<sub>1</sub> is a group of formula (d), (e) or (f)



wherein each of p and q independently is 1, 2, 3, or 4;

s is 0, 1, 2 or 3;

t is 1 or 2;

u is 0 or 1; and

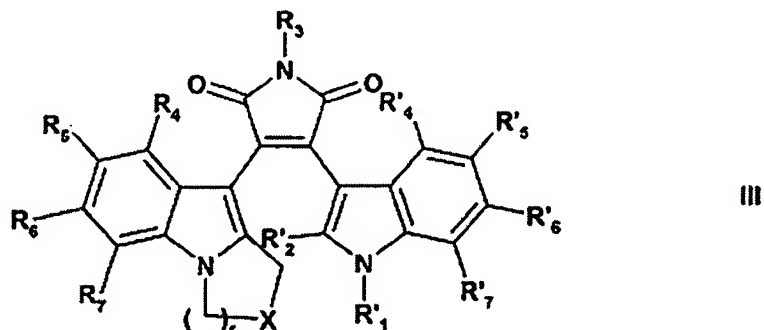
R<sub>12</sub> is hydrogen, alkyl, haloalkyl, cycloalkyl, acetyl, aryl, —CH(aryl)<sub>2</sub>, amino, monoalkylamino, dialkylamino, guanidino, —C(=N(alkoxycarbonyl))NH(alkoxycarbonyl), amidino, hydroxy, carboxy, alkoxycarbonyl or heterocyclyl;

R'<sub>1</sub> is hydrogen, C<sub>1-4</sub>alkyl, aminoalkyl, monoalkylaminoalkyl, or dialkylaminoalkyl, each of R<sub>2</sub> and R'<sub>2</sub>, independently, is hydrogen, alkyl, alkoxyalkyl, hydroxyalkyl, C<sub>1</sub>-C<sub>3</sub>alkylthio, S(O)C<sub>1</sub>-C<sub>3</sub>alkyl, CF<sub>3</sub>;

$R_3$  is hydrogen or  $\text{CH}_3\text{CO}-$ ; and

each of  $R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7$  and  $R'_7$ , independently, is hydrogen, halogen, alkyl, hydroxy, alkoxy,  $-\text{COO}(\text{C}_1\text{-C}_3\text{alkyl})$ ,  $\text{CF}_3$ , nitro, amino, acetyl amino, monoalkyl amino, dialkyl amino, alkylthio,  $\text{C}_1\text{-C}_3\text{alkylthio}$ , or  $\text{S}(\text{O})\text{C}_1\text{-C}_3\text{alkyl}$ ;

and compounds of formula III are



wherein

$R'_1$  is hydrogen,  $\text{C}_1\text{-C}_4\text{alkyl}$ , aminoalkyl, monoalkylaminoalkyl, or dialkylaminoalkyl;

$R'_2$  is hydrogen, alkyl, alkoxyalkyl, hydroxyalkyl,  $\text{C}_1\text{-C}_3\text{alkylthio}$ ,  $\text{S}(\text{O})\text{C}_1\text{-C}_3\text{alkyl}$ ,  $\text{CF}_3$

$R_3$  is hydrogen or  $\text{CH}_3\text{CO}-$ ;

each of  $R_4, R'_4, R_5, R'_5, R_6, R'_6, R_7$  and  $R'_7$ , independently, is hydrogen, halogen, alkyl, hydroxy, alkoxy,  $-\text{COO}(\text{C}_1\text{-C}_3\text{alkyl})$ ,  $\text{CF}_3$ , nitro, amino, acetyl amino, monoalkyl amino, dialkyl amino, alkylthio,  $\text{C}_1\text{-C}_3\text{alkylthio}$ , or  $\text{S}(\text{O})\text{C}_1\text{-C}_3\text{alkyl}$ ;

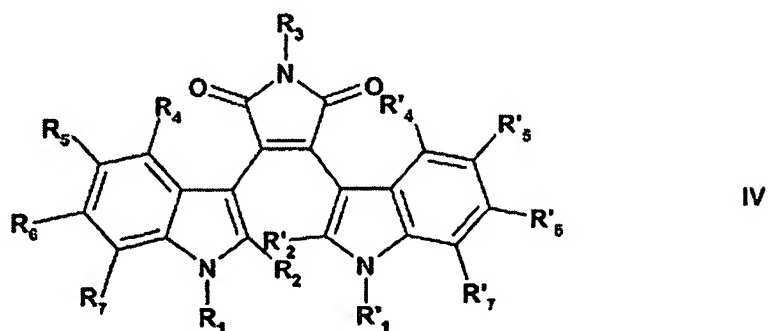
$X$  is  $\text{CR}_8\text{R}_9$  wherein  $R_8$  is  $(\text{CH}_2)_s\text{R}_{10}$  wherein  $R_9$  is  $(\text{CH}_2)_s\text{R}_{11}$ , each of  $R_{10}$  and  $R_{11}$ ,

independently, is hydroxy, alkoxy, carboxy, acyloxy, amino, monoalkyl amino, dialkyl amino, trialkyl amino, azido, acyl amino, alkoxy carbonyl, cyano, amidino, or aminocarbonyl, and  $s$

is 0, 1, 2 or 3; and

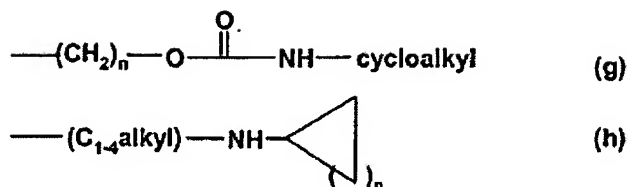
$r$  is 1, 2, or 3; and

and compounds of formula IV are



wherein

$R_1$  is alkylglycose residue or a group of formula (g) or (h)



wherein n is 1, 2, 3, 4, 5 or 6;

R'<sub>1</sub> is hydrogen, C<sub>1</sub>-C<sub>4</sub>alkyl, cyclopropylmethyl, aminoalkyl, monoalkylaminoalkyl, or, dialkylaminoalkyl;

each of R<sub>2</sub> and R'<sub>2</sub>, independently, is hydrogen, alkyl, alkoxyalkyl, hydroxyalkyl, C<sub>1</sub>-C<sub>3</sub>alkylthio, S(O)C<sub>1</sub>-C<sub>3</sub>alkyl, CF<sub>3</sub>;

R<sub>3</sub> is hydrogen or CH<sub>3</sub>CO—; and

each of R<sub>4</sub>, R'<sub>4</sub>, R<sub>5</sub>, R'<sub>5</sub>, R<sub>6</sub>, R'<sub>6</sub>, R<sub>7</sub> and R'<sub>7</sub>, independently, is hydrogen, halogen, alkyl, hydroxy, alkoxy, --COO(C<sub>1</sub>-C<sub>3</sub>alkyl), CF<sub>3</sub>, nitro, amino, acetylamino, monoalkylamino, dialkylamino, alkylthio, C<sub>1</sub>-C<sub>3</sub>alkylthio, or S(O)C<sub>1</sub>-C<sub>3</sub>alkyl.

Claim 2 (currently amended): A method according to claim 1 for the treatment ~~or prevention~~ of an autoimmune disease wherein the autoimmune disease is selected from an inflammatory bowel disease amyotrophic lateral sclerosis; multiple sclerosis; rheumatoid arthritis and hepatitis C.

Claim 3 (currently amended): A method according to claim 1, for the treatment ~~and prevention~~ of organ or tissue transplant rejection or for the prevention of graft-versus-host disease.

Claim 4 (previously presented): A method according to claim 1 wherein the protein kinase C inhibitor is a compound of formula Ia, Ib, IIa, IIIa or a pharmaceutically acceptable salt, hydrate or solvate thereof.

Claim 5 (previously presented): A method according to claim 1 wherein the protein kinase C inhibitor is 3-(1-methyl-1H-indol-3-yl)-4-[1-((1-pyridin-2-ylmethyl)-piperidin-4-yl)-1H-indol-3-yl]-pyrrole-2,5-dione, or 3-(1-methyl-1H-indol-3-yl)-4-[1-(piperidin-4-yl)-1H-indol-3-yl]-pyrrole-2,5-dione, or a pharmaceutically acceptable salt, hydrate or solvate thereof.

Claim 6 (currently amended): A pharmaceutical composition for use in the treatment ~~and prevention~~ of organ or tissue transplant rejection and for the prevention of graft-versus-host disease and/or of autoimmune diseases other than diabetes mellitus, said composition comprising a protein kinase C inhibitor of formula I, II, III or IV as defined in claim 1 or a pharmaceutically acceptable salt, hydrate or solvate thereof, together with one or more pharmaceutically acceptable diluents or carriers therefor.

Claim 7 (previously presented): A composition according to claim 6 wherein the protein kinase C inhibitor is a compound of formula Ia, Ib, IIa, IIIa or a pharmaceutically acceptable salt, hydrate or solvate thereof.

Claim 8 (previously presented): A composition according to claim 6 wherein the protein kinase C inhibitor is 3-(1-methyl-1H-indol-3-yl)-4-[1-((1-pyridin-2-ylmethyl)-piperidin-4-yl)-1H-indol-3-yl]-pyrrole-2,5-dione or 3-(1-methyl-1H-indol-3-yl)-4-[1-(piperidin-4-yl)-1H-indol-3-yl]-pyrrole-2,5-dione, or a pharmaceutically acceptable salt, hydrate or solvate thereof.

Claim 9 (previously presented): A pharmaceutical combination comprising a) a protein kinase C inhibitor of formula I, II, III or IV as defined in claim 1, or a pharmaceutically acceptable salt, hydrate or solvate thereof, and b) at least one second agent selected from an immunosuppressant and immunomodulatory drug.

Claim 10 (previously presented): A pharmaceutical combination comprising a) a protein kinase C inhibitor of formula Ia, Ib, IIa, or IIIa as defined in claim 1, or a pharmaceutically acceptable salt, hydrate or solvate thereof and b) at least one second agent selected from an immunosuppressant and immunomodulatory drug.

Claim 11 (Canceled)

Claim 12 (previously presented): A method according to claim 2 wherein the protein kinase C inhibitor is 3-(1-methyl-1H-indol-3-yl)-4-[1-((1-pyridin-2-ylmethyl)-piperidin-4-yl)-1H-indol-3-yl]-pyrrole-2,5-dione, or 3-(1-methyl-1H-indol-3-yl)-4-[1-(piperidin-4-yl)-1H-indol-3-yl]-pyrrole-2,5-dione, or a pharmaceutically acceptable salt, hydrate or solvate thereof.

Claim 13 (previously presented): A method according to claim 3 wherein the protein kinase C inhibitor is 3-(1-methyl-1H-indol-3-yl)-4-[1-((1-pyridin-2-ylmethyl)-piperidin-4-yl)-1H-indol-3-yl]-pyrrole-2,5-dione, or 3-(1-methyl-1H-indol-3-yl)-4-[1-(piperidin-4-yl)-1H-indol-3-yl]-pyrrole-2,5-dione, or a pharmaceutically acceptable salt, hydrate or solvate thereof.

Claim 14 (previously presented): A pharmaceutical combination according to claim 10 wherein a) is 3-(1-methyl-1H-indol-3-yl)-4-[1-((1-pyridin-2-ylmethyl)-piperidin-4-yl)-1H-indol-3-yl]-pyrrole-2,5-dione or 3-(1-methyl-1H-indol-3-yl)-4-[1-(piperidin-4-yl)-1H-indol-3-yl]-pyrrole-2,5-dione.